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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/270,910	03/16/99	IPSEN	H 4305/1E144-U

EXAMINER	
HUYNH, P	
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DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

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1- File Copy

PTO-90C (Rev. 2/95)
*U S GPO 2000-473-000/44602

Office Action Summary	Application No. 09/270,910	Applicant(s) IPSEN ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 40-47* is/are pending in the application.

4a) Of the above claim(s) *29-31 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-28, 32-34, and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Dr. Phuong N. Huynh, Art Unit 1644.

2. The instant application is in sequence compliance for patent applications containing amino acid sequence disclosures.

3. The Preliminary Amendments filed on 3/16/99 and 8/18/00 (Paper No. 5 & 10) are acknowledged.
The SEQ Listing has been entered.
The specification on page 40, line 2, after "protein" insert—(SEQ ID NO: 39) has NOT been entered because there is no such word on page 40, line 2.
Claims 3-4, 6, 8-10, 23, 26-29, 31-33 have been amended.
Claims 35-39 have been deleted.
Claims 40-47 have been added.
Claims 1-34, 40-47 are pending in this application.

4. Applicant's election with traverse of Group I, species Bet v1 from the taxonomic order Fagales comprising the Glu45Ser substitution in Paper No. 10 is acknowledged. The traversal is on the grounds that the claimed subject matter of Groups III, a process of using a product may be joined with the claims of Group I, directed to a product and the claims of Group II, directed to a process of making the product. This is not found persuasive because the subject matter of the three Groups is patentably distinct for reason set forth in Paper No. 9 and as shown by their divergent classification. The requirement is still deemed proper and is therefore made FINAL.
Claims 1-34, 40-47 are pending.
Claims 29-31, 40-46 and non-elected species of Group I (Claims 12, 16-28) are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.
Claims 1-15, 32-34, and 47 read on Group I, species Bet v1 from the taxonomic order Fagales comprising the Glu45Ser substitution are being prosecuted in this Office Action.

5. Applicant's amendment, filed 7/12/99 (Paper No. 6), notes that an IDS is attached to the amendment, however no such IDS appears with the instant application. Applicant is invited to resubmit such documentation to complete the instant file. The examiner apologizes for any inconvenience to applicant for having to resubmit such documentation.

6. Appropriate correction is required in the specification, (See, e.g. "IgE-binding properties of." on page 35, line 32.

7. Applicant should amend the first line of the specification to indicate the status of the priority documents, i.e., This application claims the benefit of U.S. Provisional Application No. 60/078,371 filed 03/18/1998. See MPEP 1302.04

8. The declaration, filed on 6/18/99 (Paper No. 8) is defective. A new declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.
The declaration is defective because:
The declaration does not include a claim to foreign priority as indicated in the petition on 6/18/99 (Paper No. 7) for extension of time.

9. The drawings, filed on 3/16/99, are not in compliance with 37CFR 1.84(a). Please see attached PTO 948. Appropriate correction is required.

10. Applicant should avoid the use of "novel" in the title, as patents are presumed to be novel and unobvious.

11. The Abstract in the instant case should be amended to avoid legal phraseology often used in patent claims such as "thereof".

12. For examination purposes, the term "having" is interpreted to mean "comprising".

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 32-34, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant birch pollen major allergen, Bet v I of the taxonomic order of Fagales, wherein said recombinant allergen has an amino acid substitution from glutamine to serine at position 45 of the natural Bet v I, does not reasonably provide enablement for any recombinant birch pollen allergen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification as filed does not teach all the possible amino acid substitution within the full-length sequence (159 amino acids) of the major birch allergen, Bet v I, and that after substitution will maintain both the structural limitation and functional limitation of the allergen that encode a similar polypeptide. It is well known in the art that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

The state of the prior art as exemplified by Lebecque *et al*, Gajhede *et al* and Elsayed *et al* is such that determining the IgE binding of Bet v 1 (B cell epitope) is conformational dependent by nature and the in vivo allergenic activity of the recombinant protein is unpredictable, including applicants' disclosure on page 36 bridging to page 37. Thus, the specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

14. Claims 33-34, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertain, or with which it is most nearly connected, to use the invention.

Claim 33-34, and 47 recite "a pharmaceutical composition" characterized in that comprises a recombinant allergen according to claim 1. However, the specification fails to provide any *in vivo* data, working examples, or guidance with respect to dosages as to treat, to prevent allergic reactions in a patient having allergy to pollen.

A "pharmaceutical composition" comprising "recombinant allergen" for treating allergy to pollen in the absence of in vivo data is unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, for instant, due to proteolytic degradation or immunological inactivation as a consequence of the inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, one skilled in the art could not use the invention of claim 33-34, and 47 without undue experimentation. Note, removing "pharmaceutical" from claims 33-34, and 47 would overcome the rejection since one would know how to use such composition as binding assays as disclosed in the specification.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-15, 32-34, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 and 32-34 are indefinite in the recitation of "characterized" because the metes and bounds of such conditions are ambiguous and unclear.

Claim 1 is indefinite in the recitation of "the same position in the amino acid sequence of any known homologous protein within the taxonomic order from which said naturally occurring allergen originates" since the metes and bound of the subject matter is unclear.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, because the recitation of "having essentially the same". It is suggested that applicant amend the claim to "consisting of the same α-carbon backbone".

Claim 2 recites the limitation "more than 70% identity". There is insufficient antecedent basis for this limitation in the claim.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph because the substitution language is unclear. Applicant should amend the claim to recite "Recombinant allergen according to claim 14 wherein said allergen has an amino acid substitution selected from the group consisting of substituting serine at position 45 of SEQ ID NO: 37 for glutamine, Glycine at position 108 of SEQ ID NO: 37 for Proline....."

Claim 47 is indefinite in the recitation "process according to claim 36" which was canceled.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

((b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Gajhede *et al* (Nature Structural Biology 3(12): 1040-1045, 1996; PTO 892, See entire document).

Gajhede *et al.* teaches recombinant or mutant allergen from the taxonomic order of Fagales, including birch major antigen Bet v 1, inhalation pollen allergen. The amino acid residues of the recombinant or mutant allergen are conserved with more than 70% identity with the natural allergen originated from the same taxonomic order. The recombinant or mutant allergen consists of at least one patch of amino acids wherein the patch of amino acid is a B cell epitope having solvent accessibility (contact surface) at least 20%. The path of amino acid residues are coherently connected over at least 400 $Å^2$ of the three-dimensional structure of the

allergen, at least one amino acid substitution within the patch (B cell epitope) while the overall α-carbon backbone tertiary structure of the mutant allergen is preserved. The recombinant allergen comprises a patch of amino acid having reduced IgE binding by at least 5%, preferably at least 10%, said patch of amino acid consisting of 15-25 amino acid residues wherein one or more of the amino acid residue are solvent accessible by 20-80%, 1-5 amino residues per 400 $Å^2$ in said at least one patch are substituted as encompassed by claims 1-14 (See entire document, page 1040 left column, the Beta v1 family on page 1041-1042 and Fig 2 in particular).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced recombinant allergen.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1-14, 32-33 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gajhede *et al* (Nature Structural Biology 3(12): 1040-1045, 1996; PTO 892) in view of Lowenstein *et al* (Int Arch Allergy Immunol 107: 285-289, 1995; PTO 892) and Breiteneder *et al.* (US Pat No. 6,077,517, PTO 892; See entire document).

Gajhede *et al.* teaches recombinant airborne Birch major pollen allergen comprising B cell epitope from the taxonomic order of Fagales, as discuss supra (See entire document).

Gajhede *et al.* differs from the claimed invention by not using the recombinant allergen for immunotherapy.

Lowenstein *et al.* teaches that the understanding of the B cell epitope structures is of practical importance for the use of peptides based immunotherapy in treating patients suffering allergy since even a single amino acid substitution in the recombinant Bet v1 or Car b1 can induce local perturbations on the surface of the molecule leading to differences in epitope structure; as more amino acid substitutions are introduced, the recombinant allergens show differences in their antibody binding properties. The recombinant peptide comprising the B cell

epitope after amino acid substitution would have reduce binding to IgE since IgE is a mediator of anaphylactic reaction including the release of histamine from mast cells and basophils. In other words, the antigenic sites (the IgE dominant epitope) of the various pollen allergen which have been recognized by various antibodies are likely to cross-react with the native peptide conformation. Since the specificity of antibody binding depends on the complementarity of surfaces for hydrogen binding, polar bonding as well as van der Waals contacts, mutagenized the amino acid residues within the B cell epitope would be an effective way of reducing IgE synthesis in patients suffering allergy (See entire document, Results and Discussion in particular).

Breiteneder *et al.* teaches the use of recombinant pollen allergen as a pharmaceutical composition to alleviate IgE-mediated allergic reactions encompassed by claims 31-33 and 47.

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to produce recombinant allergens for peptide based immunotherapy as taught by Breiteneder *et al* by substituting the amino acids within the B cell epitope as taught by Gajhede et al. One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to make recombinant allergen comprising amino acid substitution within the B cell epitope (IgE dominant epitope) for the same purpose of peptide based immunotherapy to improve the lives of those who suffers from bronchial asthma.

21. Claims 1, 3, 10-13, and 32-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Breiteneder *et al.* (5,693,495; PTO 892, see entire document).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
February 9, 2001

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